SUPPLEMENTAL MATERIAL

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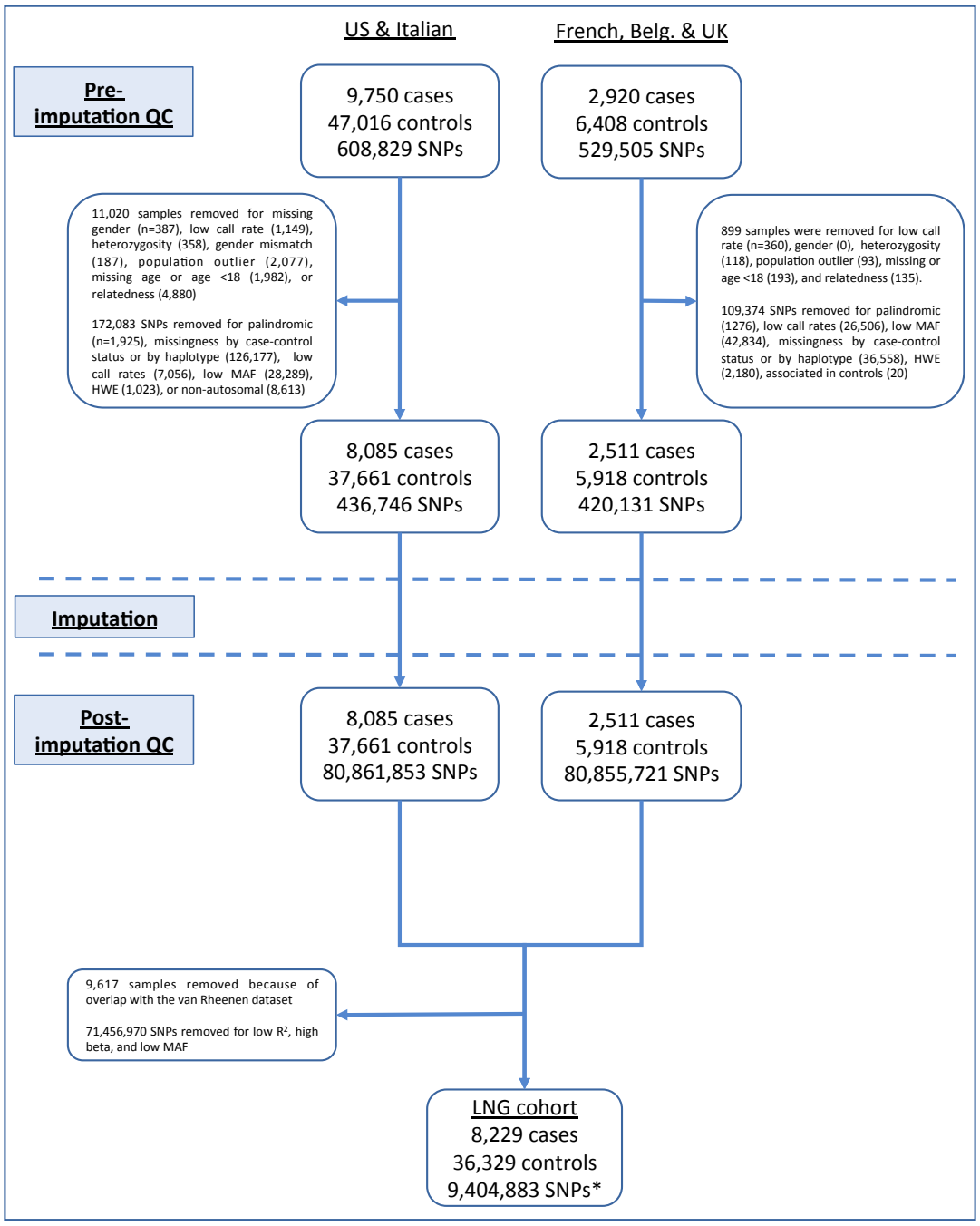

Figure S1. Related to Figure 1; Workflow showing the quality control procedures applied to the present study. *increased to 10,031,630 when merged with the Van Rheenen et al dataset; Belg., Belgium; SNP, single nucleotide polymorphism; MAF, minor allele frequency, HWE, Hardy-Weinberg equilibrium; R^2, R-square value representing imputation precision; LNG, Laboratory of Neurogenetics.

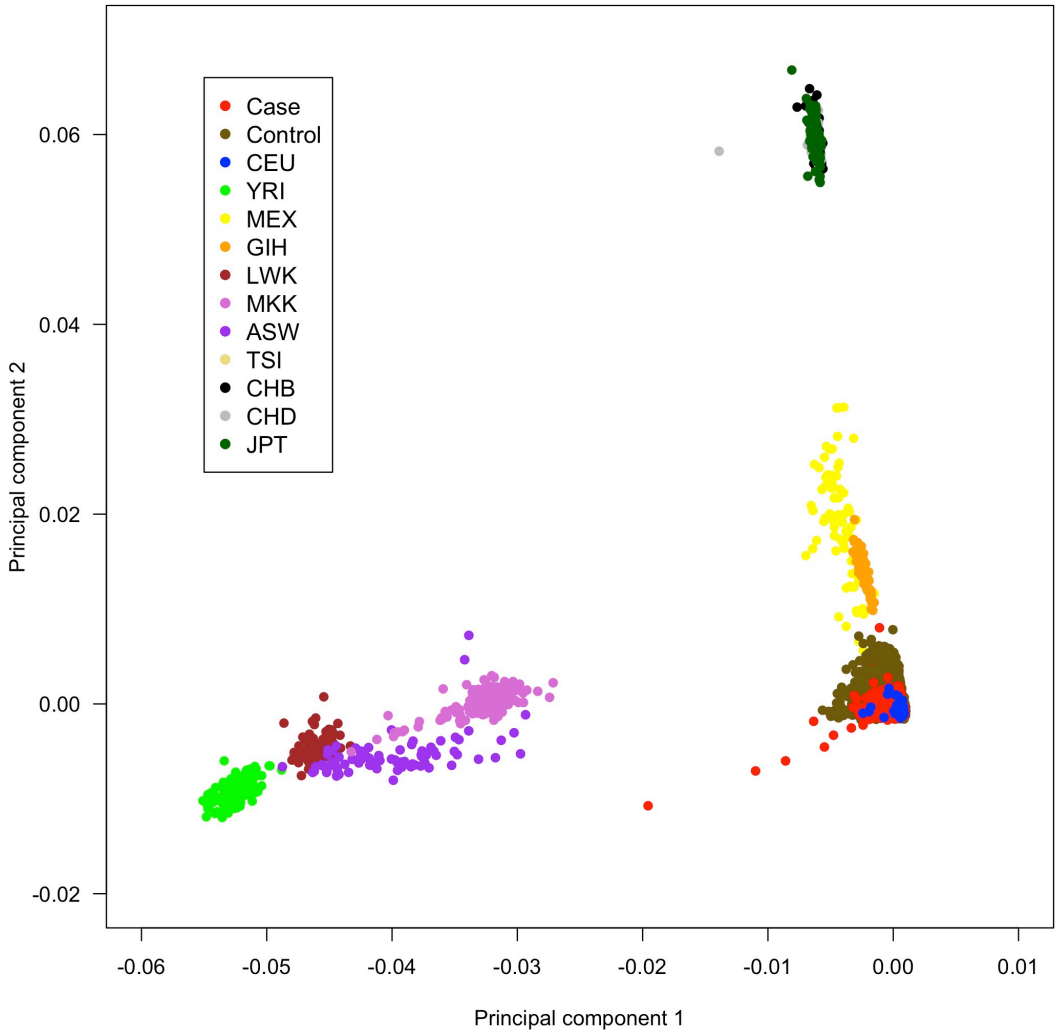

Figure S2. Related to Figure 1; Multi-dimensional scaling plot of the 44,558 genotyped samples included in analysis compared to the HapMap populations.

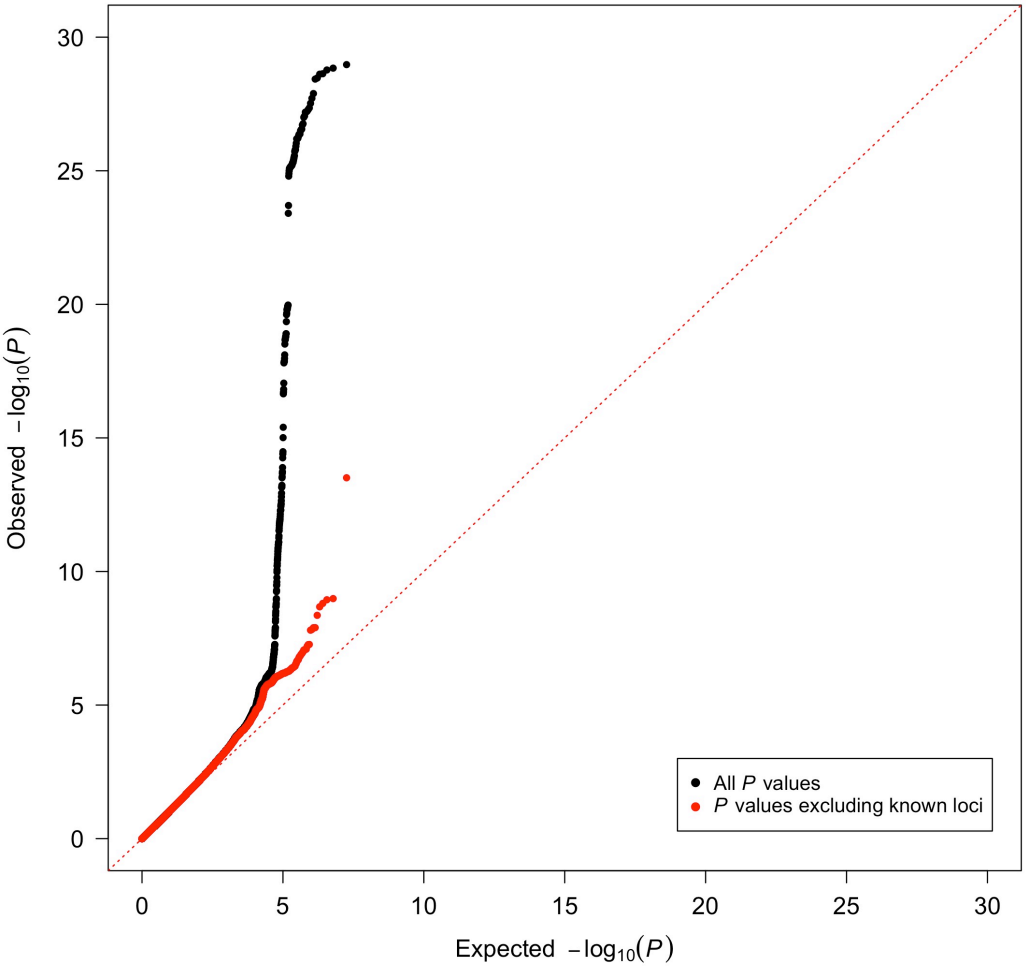

Figure S3. Related to Figure 1; Quartile-Quartile plot of *P*-values from the meta-analysis based on logistic regression analysis. The black curve represents all SNPs, and the red curve represent SNPs after excluding variants within +/- 500 kilobases of the *C9orf72* and the *UNC13A* loci. Raw genome inflation factor (λ) was 1.042 and adjusted λ scaled to 1,000 cases and 1,000 controls was 1.001 based on the entire SNP dataset.

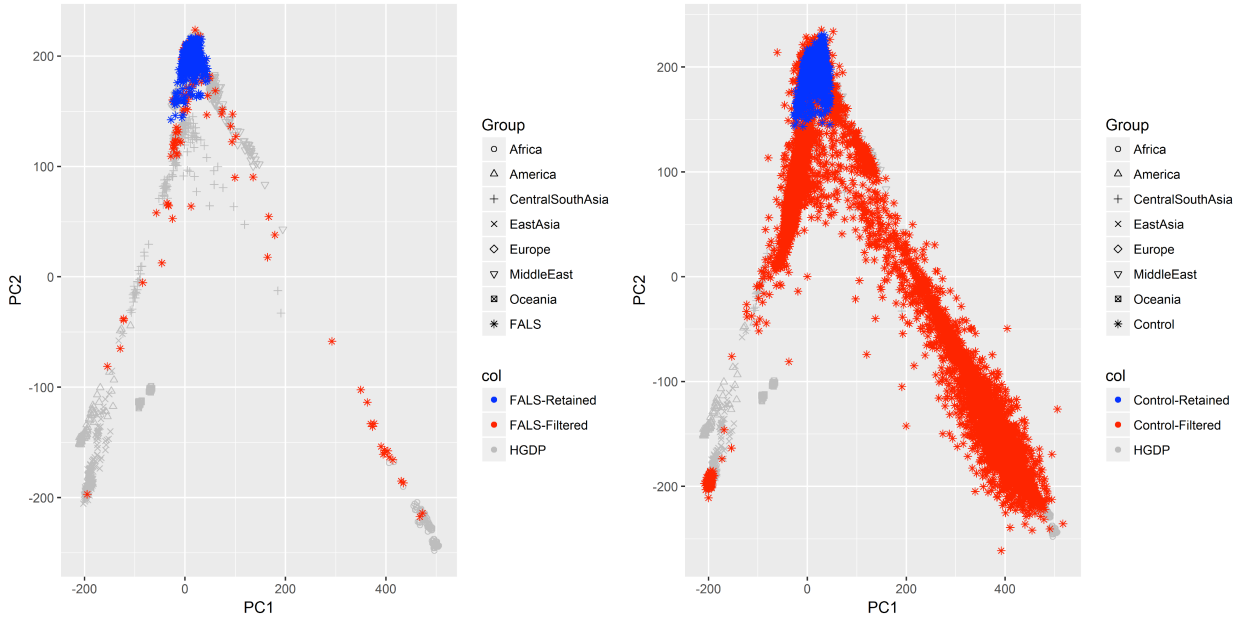

Figure S4. Related to Figure 3; Principal components analysis of samples included in the RVB analysis compared to the Human Diversity Panel. Ancestry filtering of the FALS discovery cohort was performed as follows: LASER was used to generate PCA coordinates for samples from the Human genome diversity panel (HGDP). Samples from the FALS discovery cohort were then mapped to this reference co-ordinate space. The discovery cohort was restricted to cases and controls occurring within 3 standard deviations of the mean for European HGDP samples along principal components 1-4.

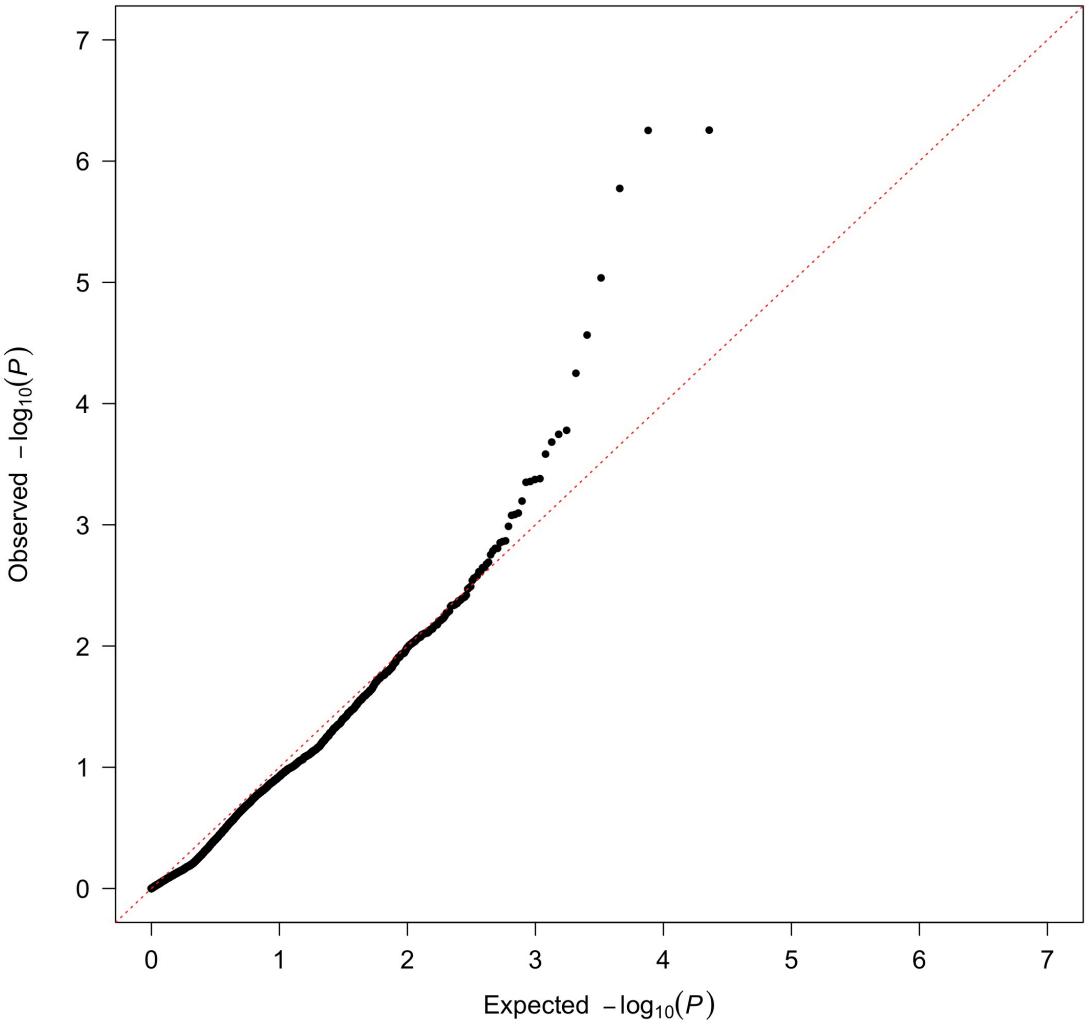

Figure S5. Related to Figure 3; Quartile-Quartile plot of P values from the gene-based rare variant burden analysis of exome data. The genomic inflation factor ($\lambda = 0.93$) was calculated based on the entire gene dataset.

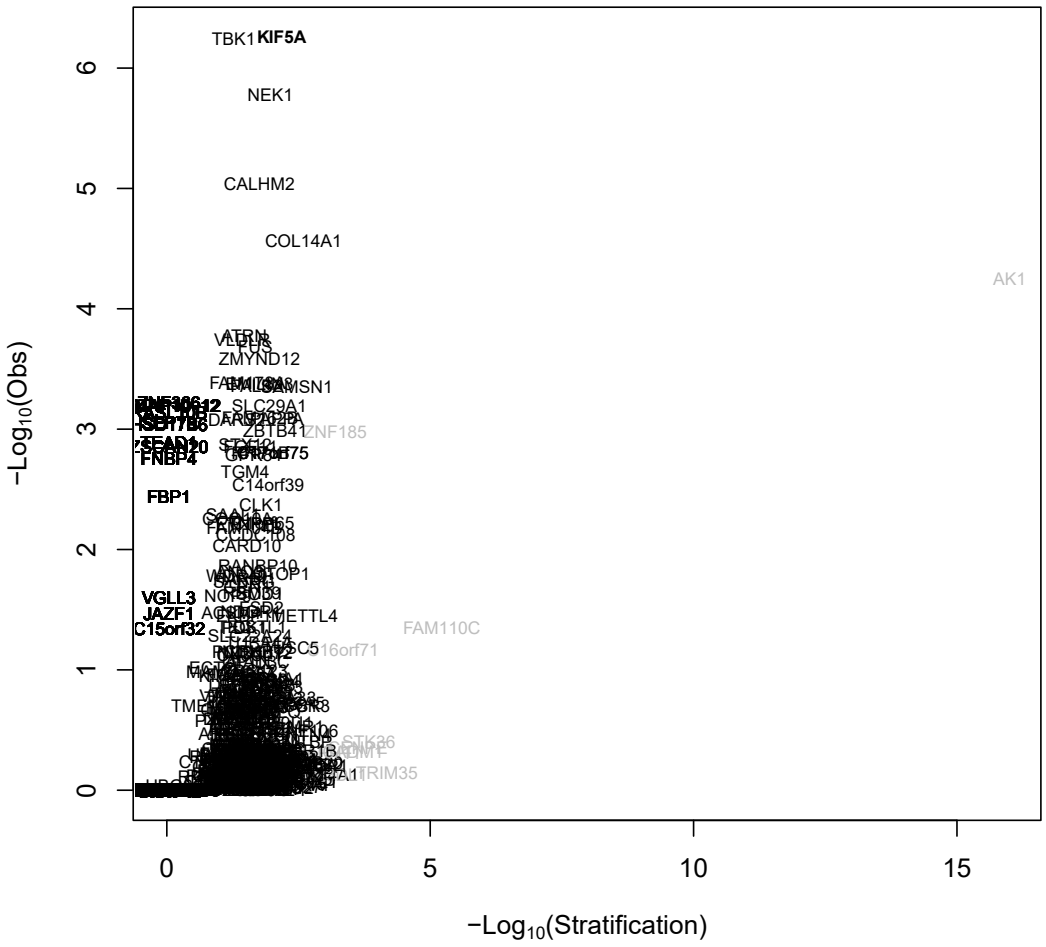

Figure S6. Related to Figure 3; Control-control analyses. *P* values from RVB analysis of FALS cases versus controls (y-axis) are plotted against minimum *P* values from RVB analyses of candidate batch effects (x-axis). To assess the potential impact of batch effects, the sample cohort was divided into 28 pseudo case-control groups based on the sequencing center or associated dbGaP project. Loci showing possible association with non-ALS related batch effects are coloured light grey. No evidence of confounder bias was observed for *KIF5A* or previously reported ALS genes.

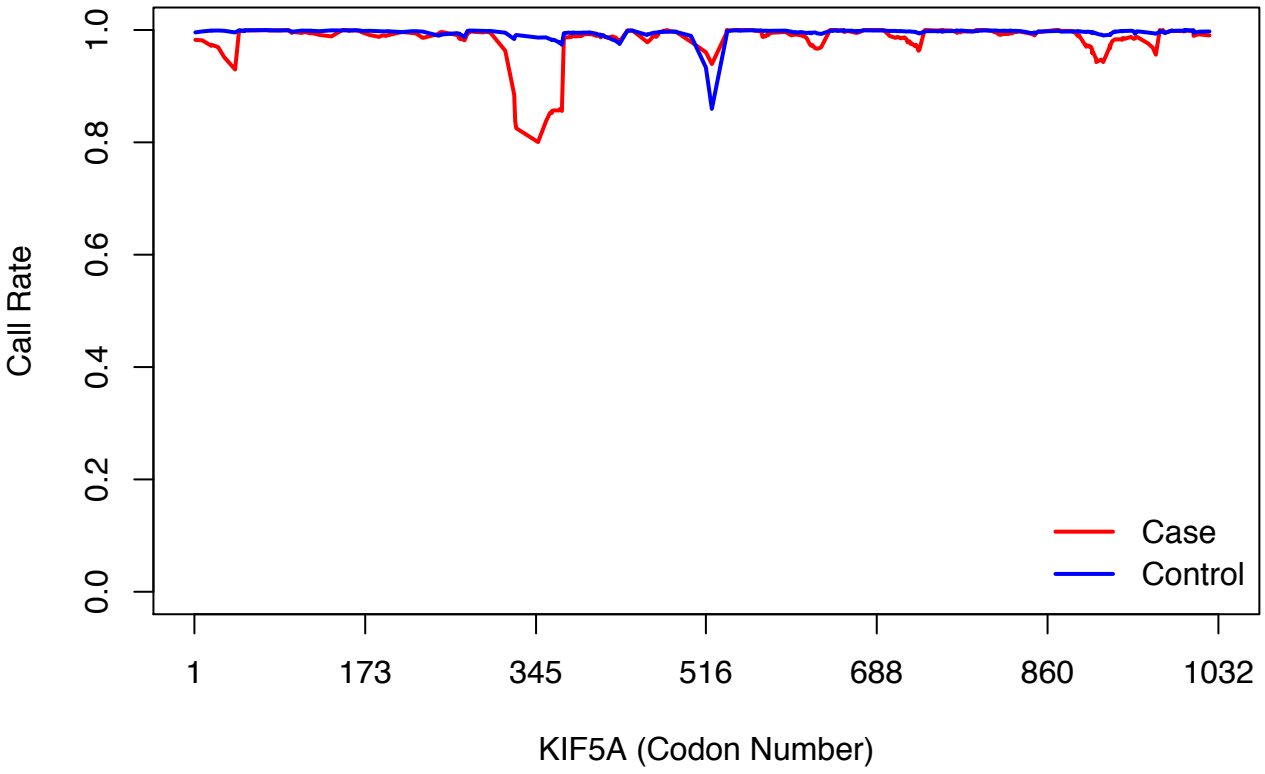

Figure S7. Related to Fgure 3; Plot of variant call rates across the KIF5A protein-coding region in FALS versus controls analyzed by RVB testing.

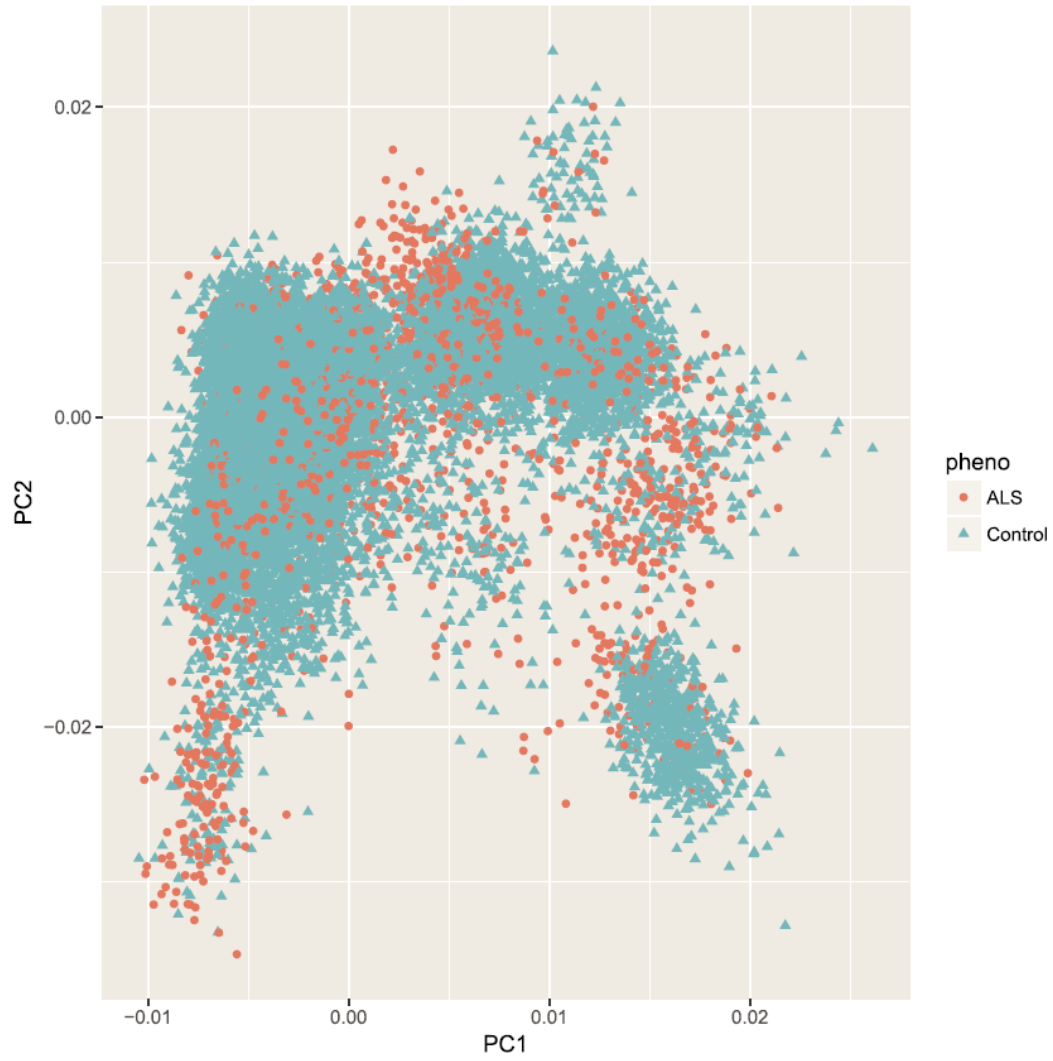

Figure S8. Related to Figure 2; Principal components analysis of samples included in *KIF5A* replication cohort.

Table S1. Related to Figure 1; Demographics and baseline characteristics of patients diagnosed with ALS and control individuals included in the GWAS analysis.

	US		Italian		UK		French & Belgian		Total cohort	
	cases	controls	cases	controls	cases	controls	cases	controls	cases	controls
Sample number	3,777	33,365	2,853	2,143	449	226	1,150	595	8,229	36,329
Female (%)	1,515 (40.1)	23,870 (71.5)	1,239 (43.4)	896 (41.8)	193 (43.0)	109 (48.2)	486 (42.3)	422 (70.9)	3,433 (41.7)	25,297 (69.6)
Age (SD)	58.1 (12.3)	64.2 (13.3)	61.8 (11.8)	50.6 (17.4)	60.3 (12.8)	57.0 (0.0)	60.5 (12.6)	66.9 (16.8)	59.8 (12.3)	63.4 (13.9)
Bulbar-onset* (%)	963 (25.5)	-	741 (26.0)	-	141 (31.4)	-	357 (31)	-	2,202 (26.8)	-
Family history† (%)	458 (12.1)	-	248 (8.7)	-	54 (12.0)	-	195 (17.0)	-	955 (11.6)	-

SD, standard deviation. *Data not available for site of symptom onset for 199 patients. †Data not available for familial history of 154 patients.

Table S2. Related to Figure 1; DbGaP studies contributing to the GWAS analysis.

Accession Number	Study	Sample number	Females (%)	Average age (SD)	Genotyping platform	Ascertainment criteria
phs000001	NEI Age-Related Eye Disease Study (AREDS)	1,644	959 (58.3)	68.2 (4.8)	HumanOmni2.5	Population controls
phs000007	Framingham Cohort	1,298	718 (55.3)	75.7 (8.6)	HumanOmni5	Population controls
phs000187	High Density SNP Association Analysis of Melanoma	1,027	414 (40.3)	51.3 (12.6)	HumanOmniExpress	Population controls
phs000196	CIDR: The NeuroGenetics Research Consortium Parkinson's Disease Study	10	6 (60)	74.3 (18.6)	HumanOmni1	Population controls
phs000292	GENEVA Genetics of Early Onset Stroke (GEOS) Study	89	0 (0)	41.5 (6.4)	HumanOmni1	Population controls
phs000304	Genes and Blood Clotting Study (GABC)	403	259 (64.3)	21.6 (3.3)	HumanOmni1	Population controls
phs000315	Woman's Health Initiative (WHI GARNET)	4,206	4206 (100)	65.7 (6.9)	HumanOmni1	Population controls
phs000368	Polycystic Ovary Syndrome Genetics (POLYGEN)	2,974	2973 (100)	46.8 (15.2)	HumanOmniExpress	Population controls
phs000372	Alzheimer's Disease Genetics Consortium Genome Wide Association Study	533	335 (62.9)	75.8 (9)	HumanOmniExpress	Population controls
phs000394	Autopsy-Confirmed Parkinson Disease GWAS Consortium (APDGC)	299	152 (50.8)	82.1 (12.6)	HumanOmni1	Population controls
phs000397	NIA Long Life Family Study (LLFS)	1,804	957 (53)	65.9 (12.3)	HumanOmni2.5	Population controls
phs000404	The Genetic Architecture of Smoking and Smoking Cessation	81	50 (61.7)	36.6 (5.9)	HumanOmni2.5	Population controls
phs000421	A Genome-Wide Association Study of Fuchs' Endothelial Corneal Dystrophy	497	294 (59.2)	70.4 (10.2)	HumanOmni2.5	Population controls
phs000428	Health and Retirement Study (HRS)	9,394	5437 (57.9)	68.4 (9.4)	HumanOmni2.5	Population controls
phs000615	NINDS Stroke Genetics Network (SiGN)	743	416 (56)	56 (16.1)	HumanOmni5	Population controls
phs000675	GWAS on Selected WHI Hormone Trial European Americans	5,626	5626 (100)	68 (5.9)	HumanOmni1	Population controls
phs000801	NCI Non-Hodgkin Lymphoma GWAS	1,544	790 (51.2)	58.4 (11.6)	HumanOmniExpress	Population controls
phs000869	Barrett's and Esophageal Adenocarcinoma Genetic Susceptibility Study (BEAGESS)	1,174	271 (23.1)	61.3 (10.9)	HumanOmni1	Population controls

Table S3. Related to Figure 1; SNPs achieving genome-wide significance in the GWAS analysis.

SNP Information				Present Study (8,229 Cases / 36,329 Controls)			Van Rheenen *et al.* (12,577 Cases / 23,475 Controls)			Combined Discovery Set (20,806 Cases / 59,804 Controls)			
SNP	**Chr**	**Position**	**Gene**	**Beta [SE]**	**OR [95% CI]**	***P***	**Beta [SE]**	**OR [95% CI]**	***P***	**I^2**	**Beta [SE]**	**OR [95% CI]**	***P***
Novel Loci													
rs117027576	12	57,316,603	*KIF5A*	0.373 [0.096]	1.45 [1.20-1.76]	$1.1x10^{-4}$	0.286 [0.070]	1.33 [1.16-1.53]	$4.3x10^{-5}$	25.6	0.316 [0.057]	1.37 [1.23-1.54]	$2.3x10^{-8}$
rs118082508	12	57,318,819	*KIF5A*	0.374 [0.096]	1.45 [1.20-1.76]	$1.0x10^{-4}$	0.288 [0.070]	1.33 [1.16-1.53]	$3.8x10^{-5}$	25.8	0.317 [0.051]	1.37 [1.23-1.54]	$2.0x10^{-8}$
rs113247976*	12	57,975,700	*KIF5A*	0.381 [0.086]	1.46 [1.23-1.74]	$9.2x10^{-6}$	0.288 [0.066]	1.33 [1.17-1.52]	$1.1x10^{-5}$	0.0	0.322 [0.052]	1.38 [1.24-1.53]	$6.4x10^{-10}$
rs116900480	12	58,656,105	*KIF5A*	0.354 [0.083]	1.42 [1.21-1.68]	$1.9x10^{-5}$	0.294 [0.065]	1.34 [1.18-1.53]	$7.1x10^{-6}$	0.0	0.317 [0.051]	1.37 [1.24-1.52]	$6.6x10^{-10}$
rs142321490	12	58,676,132	*KIF5A*	0.357 [0.082]	1.43 [1.21-1.68]	$1.5x10^{-5}$	0.292 [0.066]	1.34 [1.18-1.53]	$8.0x10^{-6}$	0.0	0.317 [0.056]	1.37 [1.24-1.52]	$6.1x10^{-10}$
Previously Published Loci													
rs10463311	5	150,410,835	*TNIP1*	-0.065 [0.024]	0.94 [0.89-0.98]	$7.8x10^{-3}$	-0.100 [0.020]	0.91 [0.87-0.94]	$8.5x10^{-7}$	0.0	-0.085 [0.016]	0.92 [0.89-0.95]	$4.0x10^{-8}$
rs3849943	9	27,543,382	*C9orf72*	-0.17 [0.024]	0.84 [0.80-0.88]	$1.4x10^{-12}$	-0.181 [0.020]	0.83 [0.80-0.87]	$4.0x10^{-19}$	0.0	-0.176 [0.016]	0.84 [0.81-0.86]	$3.8x10^{-30}$
rs74654358	12	64,881,967	*TBK1*	0.182 [0.058]	1.20 [1.07-1.34]	$1.6x10^{-3}$	0.206 [0.042]	1.23 [1.13-1.34]	$7.7x10^{-7}$	0.0	0.198 [0.034]	1.22 [1.14-1.30]	$4.7x10^{-9}$
rs12973192	19	17,753,239	*UNC13A*	-0.149 [0.026]	0.86 [0.82-0.91]	$1.3x10^{-8}$	-0.106 [0.019]	0.9 [0.87-0.93]	$2.4x10^{-8}$	38.6	-0.121 [0.015]	0.89 [0.86-0.91]	$3.9x10^{-15}$
rs75087725	21	45,753,117	*C21orf2*	0.687 [0.162]	1.99 [1.44-2.75]	$2.2x10^{-5}$	0.479 [0.074]	1.61 [1.39-1.87]	$8.7x10^{-11}$	31.1	0.515 [0.067]	1.67 [1.46-1.91]	$1.8x10^{-14}$

Position is based on Human Genome Assembly build 37. Nearest gene or previously published gene names are included. Chr, chromosome; SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval; *, rs113247976 represents the p.Pro986Leu variant in *KIF5A* (NM_004984.2).

Table S4. Related to Figure 1; Suggestive SNPs with *P* values less than 5.0x10-7 in the GWAS analyses.

SNP Information				Present Study (8,229 Cases / 36,329 Controls)				Van Rheenen *et al.* (12,577 Cases / 23,475 Controls)				Combined Discovery Set (20,806 Cases / 59,804 Controls)			
SNP	**Chr**	**Position**	**Gene**	**Case MAF**	**Control MAF**	**OR [95% CI]**	***P***	**Case MAF**	**Control MAF**	**OR [95% CI]**	***P***	**Case MAF**	**Control MAF**	**OR [95% CI]**	***P***
rs17070492	8	2,420,855	*LOC101927815*	10.01%	9.76%	1.10 [1.02-1.18]	$1.3x10^{-2}$	9.17%	10.09%	1.16 [1.09-1.23]	$1.3x10^{-6}$	9.50%	9.89%	1.13 [1.08-1.19]	$1.0 x10^{-7}$
rs10139154	14	31,147,498	*SCFD1*	34.10%	31.30%	1.07 [1.03-1.12]	$2.1x10^{-3}$	33.76%	31.17%	1.08 [1.04-1.12]	$1.9x10^{-5}$	33.90%	31.25%	1.08 [1.05-1.11]	$1.4 x10^{-7}$
rs10143310	14	92,540,381	*ATXN3*	24.85%	24.36%	1.09 [1.04-1.015]	$3.3x10^{-4}$	24.04%	22.95%	1.08 [1.04-1.13]	$2.6x10^{-4}$	24.36%	23.81%	1.09 [1.05-1.12]	$3.2 x10^{-7}$
rs9901522	17	14,673,934	*PMP22*	7.08%	6.31%	1.16 [1.06-1.26]	$5.2x10^{-4}$	6.87%	5.97%	1.16 [1.08-1.24]	$4.6x10^{-5}$	6.95%	6.18%	1.16 [1.10-1.22]	$8.6 x10^{-8}$

Table S5. Related to Figure 3; DbGaP/EGA studies contributing to the RVB analysis.

Accession Number	Study	Sample number	Females (%)
phs000179	Genetic Epidemiology of COPD (COPDGene)	2	100%
phs000254	NHLBI GO-ESP: Lung Cohorts Exome Sequencing Project (Cystic Fibrosis)	238	49.6%
phs000281	NHLBI GO-ESP: Women's Health Initiative Exome Sequencing Project (WHI) - WHISP	1904	100%
phs000290	NHLBI GO-ESP: Lung Cohorts Exome Sequencing Project (Pulmonary Arterial Hypertension)	73	82.2%
phs000291	NHLBI GO-ESP: Lung Cohorts Exome Sequencing Project (Lung Health Study of COPD)	332	37%
phs000296	NHLBI GO-ESP: Lung Cohorts Exome Sequencing Project (COPDGene)	285	52.6%
phs000307	NHLBI Framingham Heart Study Allelic Spectrum Project	1317	51.6%
phs000347	NHLBI GO-ESP: Family Studies (Aortic Disease)	29	34.5%
phs000354	NHLBI GO-ESP Family Studies: Pulmonary Arterial Hypertension	9	88.9%
phs000362	NHLBI GO-ESP: Family Studies: (Familial Atrial Fibrillation)	12	16.7%
phs000398	NHLBI GO-ESP: Heart Cohorts Exome Sequencing Project (ARIC)	800	54.6%
phs000400	NHLBI GO-ESP: Heart Cohorts Exome Sequencing Project (CHS)	186	28%
phs000401	NHLBI GO-ESP: Heart Cohorts Exome Sequencing Project (FHS)	348	36.8%
phs000402	NHLBI GO-ESP: Heart Cohorts Exome Sequencing Project (JHS)	296	58.8%
phs000403	NHLBI GO-ESP: Heart Cohorts Exome Sequencing Project (MESA)	259	45.2%
phs000422	NHLBI GO-ESP: Lung Cohorts Exome Sequencing Project (Asthma)	189	65.1%
phs000498	Jackson Heart Study Allelic Spectrum Project	1629	63.8%
phs000518	NHLBI GO-ESP Family Studies: Idiopathic Bronchiectasis	24	70.8%
phs000572	Alzheimer's Disease Sequencing Project (ADSP)	4655	58.8%
phs000632	NHLBI GO-ESP: Family Studies (Hematological Cancers)	19	36.8%
phs000651	Building on GWAS: the U.S. CHARGE consortium - Sequencing (CHARGE-S): FHS	550	61.5%
phs000667	Building on GWAS for NHLBI-Diseases: The U.S. CHARGE Consortium - Sequencing (CHARGE-S): CHS	1209	52.9%
phs000668	Building on GWAS: the U.S. CHARGE consortium - Sequencing (CHARGE-S): ARIC	5497	58.5%
phs000744	Yale Center for Mendelian Genomics (Y CMG)	1944	44.7%
phs000806	MIGen_ExS: Ottawa Heart Study	1966	33.1%
phs000814	MIGen_ExS: Italian Atherosclerosis Thrombosis and Vascular Biology	3591	11.3%
phs000908	Identification of Rare Variants in PD through Whole Exome Sequencing	105	66.7%
phs000917	MIGen_ExS: PROMIS	7298	17.9%
phs001000	MIGen_ExS: U. of Leicester	1081	0%
phs001101	MIGen_ExS: MDC	1075	44.7%
EGAO00000000079	UK10K	4062	65%
phs000101	NIH Exome Sequencing of Familial Amyotrophic Lateral Sclerosis Project	201	45%

Table S6. Related to Figure 2, 3; Quality control filtering of the FALS discovery and *KIF5A* replication cohorts.

FALS discovery cohort

Cohort	Cases	Controls
Initial Sample Set	1,463	41,410
Post HGDP Continental Ancestry Filter	1,397	24,563
Post Call Rate Filter	1,331	20,789
Post Heterozygosity Filter	1,319	20,664
Post Relatedness Filter	1,138	19,494

rs113247976 replication cohort (FALS discovery + ALS WXS/WGS replication cohort)

Cohort	Cases	Controls
Initial Sample Set	12,180*	21,533**
Post Call Rate Filter	11,916	21,050
Post Heterozygosity Filter	11,721	21,028
Post Ancestry Filter (PCA)	11,373	21,009
Post Relatedness & GWAS Checksum Filter	4,160	18,650

* All 1,138 FALS passing QC in FALS discovery cohort + 11,042 additional ALS WXS/WGS cases

** All 19,494 controls passing QC in FALS discovery cohort + 2,039 additional WXS/WGS controls

LOF screen (ALS WXS/WGS replication cohort)

Cohort	Cases	Controls
Initial Sample Set	11,042*	2,039**
Post Call Rate Filter	10,741	2,039
Post Heterozygosity Filter	10,549	2,026
Post Ancestry Filter (PCA)	10,201	2,008
Post Relatedness	9,046	1,955

* 11,042 additional ALS WXS/WGS cases not included in FALS discovery cohort

** 2,039 additional WXS/WGS controls not included in FALS discovery cohort

See Experimental Procedures for further details on filtering parameters.

Table S7. Related to Figure 3; RVB analysis according to mutation type across KIF5A and within gene sub-domains.

Analysis	FALS	Control	OR (95% CI)	*P*
Missense - Full CDS	9 (0.79%)	80 (0.41%)	1.93 (0.915-3.60)	$8.09x10^{-2}$
Missense - Motor Domain	3 (0.26%)	18 (0.09%)	3.27 (0.86-9.25)	$7.74x10^{-2}$
Missense - Microtubule Binding Domain	2 (0.18%)	8 (0.04%)	5.07 (0.95-18.52)	$5.57x10^{-2}$
Missense - Coiled-Coil Domain	3 (0.26%)	55 (0.28%)	1.01 (0.28-2.60)	$9.83x10^{-1}$
Missense - C-Terminal Domain	3 (0.26%)	7 (0.04%)	7.23 (1.74-24.55)	$9.41x10^{-3}$
Loss of Function	6 (0.53%)	3 (0.02%)	32.07 (9.05-135.27)	$5.55x10^{-7}$
Loss of Function (including frameshifts)	8 (0.70%)	3 (0.02%)	41.16 (12.61-167.57)	$3.77x10^{-9}$

FALS, familial ALS; OR, odds ratio; 95% CI, 95% confidence interval; CDS, coding sequence

Table S8. Related to Figure 3; Clinical information of probands and relatives carrying *KIF5A* LOF variants.

Position	Variant	Relation to Proband	DNA Available	Exon	cDNA	Description	Gender	Age of Onset (years)	Site of Onset	Survival (months)	Alive
57,975,729	GA>A	Proband	Y	26	c.2987delA	p.Asp996fs	M	45	n/a	n/a	n/a
57,976,382	C>T	Proband	Y	27	c.2993-3C>T	5' Splice Junction	M	29	L	>264	Y
57,976,382	C>T	Sister	Y	27	c.2993-3C>T	5' Splice Junction	F	52	L	84	N
57,976,382	C>T	Brother	Y	27	c.2993-3C>T	5' Splice Junction	M	18	L	324	N
		Brother	N				M	n/a	L	n/a	N
57,975,731	CA>C	Sporadic	Y	26	c.2989delA	p.Asn997fs	F	50	L	>96	Y
57,976,384	G>A	Sporadic	N	27	c.2993-1G>A	5' Splice Junction	n/a	52	B	n/a	n/a
57,976,385	GA>G	Proband	Y	27	c.2996delA	p.Asn999fs	M	42	L	>12	Y
		Brother	N				M	38	n/a	24	N
57,976,411	A>G	Proband	Y	27	c.3019A>G	p.Arg1007Gly	F	53	L	45	N
57,976,412	G>A	Proband	Y	27	c.3020G>A	p.Arg1007Lys	M	50	L	>108	Y
57,976,412	G>A	Proband	Y	27	c.3020G>A	p.Arg1007Lys	F	50	n/a	>240	Y
57,976,413	G>A	Proband	Y	27	c.3020+1G>A	3' Splice Junction	M	45	B	>220	Y
		Parent	N				n/a	47	n/a	156	N
		Uncle/Aunt	N				n/a	57	n/a	144	N
		Uncle/Aunt	N				n/a	55	n/a	121	N
		Uncle/Aunt	N				n/a	46	n/a	24	N
57,976,414	T>A	Proband	Y	27	c.3020+2T>A	3' Splice Junction	M	46	B	124	N
57,976,414	T>A	Brother	Y	27	c.3020+2T>A	3' Splice Junction	M	48	L	117	N
		Mother	N				F	35	L	144	N
57,976,415	A>G	Proband	Y	27	c.3020+3A>G	3' Splice Junction	M	50	B	54	N

All mutations were heterozygous; Genomic coordinates are based on Human Genome Assembly build 37; Protein change is based on transcript NM_004984.3; n/a, not applicable or not availabl